Paragraph 5: Objection to the Drawings

The Examiner continues to maintain that the Formal Drawings filed on March 30, 2001 have been objected to by the Draftsperson under 37 C.F.R. §§ 1.84 or 1.152.

Applicant notes that Form PTO 948 attached to the Office Action dated December 12, 2001 (Paper No. 14) indicates that the Draftsperson reviewed the drawings filed on July 21, 2000, and not the Formal Drawings filed on March 30, 2001. Applicant respectfully requests that the Draftsperson consider the Formal Drawings filed on March 30, 2001.

Alternatively, Applicant requests a copy of Form PTO 948 that indicates the Draftsperson's specific objections to the Formal Drawings filed on March 30, 2001 so that the appropriate corrections can be made.

Paragraph 6: Information Disclosure Statement

Applicant acknowledges a listing of references in the specification is not a proper Information Disclosure Statement.

Applicant acknowledges that the Information Disclosure Statement (IDS) filed on March 30, 2001 has been considered by the Examiner.

Paragraph 7: Objection to Claim 34 Under 37 C.F.R. § 1.75(c)

Claim 34 stands objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner contends that "Claim 34 necessitates the analysis of all four markers via steps 1-6" but "claim 21 merely requires detection of brain endothelial cell membrane and one other marker." Applicant respectfully disagrees with this assessment.

Claim 21 requires analyzing body fluid to detect the presence of one or more ischemic marker proteins and analyzing body fluid to detect the presence of a brain endothelial cell membrane protein. Claim 34 entails assessing patient condition by concluding from the results of the analyses of Claim 21 the type of brain injury that has occurred. Moreover, Claim 34, as amended in the Amendment After Final, filed on March 18, 2002, does not recite "steps 1-6". In accordance with 37 C.F.R. § 1.114, entry and consideration of this Amendment After Final were requested in the Request for Continued Examination (RCE) filed on June 12, 2002.

Notwithstanding the above, in an effort to advance prosecution in the subject application, Claim 34 has been canceled.

Paragraph 8: Rejection of Claims 21, 23-34, 44-45 and 54-60 Under 35 U.S.C. § 112, Second Paragraph

Claims 21, 23-34, 44-45 and 54-60 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. A discussion of each of the specific rejections made by the Examiner follows:

A. Claim 21 has been rejected as vague and indefinite in the recitation of a "method for the differential diagnosis of ischemic and hemorrhagic cerebral events" because, in the Examiner's assessment, it is unclear "how only two markers will measure differential ischemic and hemorrhagic cerebral events." The Examiner alleges that, for example, "if a brain endothelial cell membrane protein (like Tm) identifying a lucunar [sic] infarct is measured along with only NSE which indicates TIA (transitory ischemic attack)", it is unclear how "these two proteins distinguish between ischemic and hemorrhage cerebral events." Applicant respectfully disagrees with the Examiner's assessment that Claim 21 is vague and indefinite.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S. P.Q. 2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 0947 (1987).

Figure 2 of the application is a flow chart illustrating how data from an analysis of a body fluid to detect the presence and concentration of specific marker proteins provides information as to the type of cerebral event, the onset of occurrence and the extent of brain damage. For example, as the Examiner acknowledges, Figure 2 reveals that detecting the presence of *a brain endothelial cell membrane protein alone* in the body fluid of a patient indicates that the patient condition is a lucunar infarct (i.e., an ischemic cerebral event). Figure 2 reveals that detecting the

presence *NSE alone* in the body fluid indicates that the patient condition is a TIA (i.e., an ischemic cerebral event). Figure 2 also reveals that detecting the presence of *both* a brain endothelial cell membrane protein and NSE indicates that the patient condition is an evolving cerebral infract (i.e., an ischemic cerebral event). The skilled artisan understands that a lucunar infarct, a TIA and an evolving cerebral infarct are all ischemic cerebral events.

Additionally, Figure 2 reveals that detecting the presence of NSE together with the presence of any one of MBP, S100 or a brain endothelial cell membrane protein indicates that the patient condition is an ischemic cerebral event. Figure 2 reveals that detecting the presence of a brain endothelial cell membrane protein together with the presence of any one of MBP, NSE or S100 indicates that the patient condition is an ischemic cerebral event. Figure 2 reveals that detecting the presence of S100 alone indicates that the patient condition is an ischemic cerebral event. Figure 2 further reveals that detecting the presence of S100 together with the presence of elevated levels of NSE and normal levels of a brain endothelial cell membrane protein indicates that the patient condition is an ischemic cerebral event. Figure 2 reveals that detecting the presence of S100 either alone or together with the presence of elevated levels of NSE or a brain endothelial cell membrane indicates that the patient condition is an ischemic cerebral event.

In contrast, Figure 2 reveals that detecting the presence of MBP at a level 200 times normal or greater indicates that the patient condition is a hemorrhagic cerebral event. Figure 2 also reveals that detecting elevated levels both S100 and NSE together with the presence of normal levels of both MBP and a brain endothelial cell membrane protein indicates that the patient condition is a hemorrhagic cerebral event. Figure 2 further reveals that detecting the presence of elevated levels of both S100 and MBP indicates that the patient condition is a hemorrhagic cerebral event.

Accordingly, one skilled in the art would know how to distinguish between an ischemic cerebral event and a hemorrhage cerebral event using data obtained from an analysis of a body fluid to detect the presence and concentration of one or more specific ischemic marker proteins and a brain endothelial cell membrane protein. As such, Claim 21 is definite and the metes and bounds are clear, when read in light of the specification.

Reconsideration and withdrawal of this rejection of Claim 21 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

B. Claims 26 and 27 have been rejected as vague and indefinite because, in the Examiner's assessment, it is not clear as to what "cell type specific" refers to in the claims.

Respectfully, Claim 26 had been amended in the Amendment After Final, filed on March 18, 2002, to recite that the secondary marker protein is from the same cell type as the ischemic marker protein detected. The amendment was not intended to narrow the scope of the claims. In accordance with 37 C.F.R. § 1.114, entry and consideration of this Amendment After Final were requested in the RCE filed on June 12, 2002. It is believed that entry of the Amendment After Final obviates this rejection.

C. Claim 34 has been rejected as vague and indefinite because, in the Examiner's assessment, it appears that NSE, MBP and S100 are but Claim 34 depends from Claim 21, which merely requires that one of these proteins be detected. Applicant respectfully disagrees with this assessment.

As discussed above, Claim 21 requires analyzing body fluid to detect the presence of one or more ischemic marker proteins and analyzing body fluid to detect the presence of a brain endothelial cell membrane protein. Claim 34 entails assessing patient condition by concluding from the results of the analyses of Claim 21 the type of brain injury that has occurred.

Notwithstanding the above, in an effort to advance prosecution in the subject application, Claim 34 has been canceled.

Paragraph 9: Rejection of Claims 21, 23-33, 44-45 and 60 Under 35 U.S.C. § 112, First Paragraph

Claims 21, 23-33, 44-45 and 50 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification "while being enabling for a method that differentially diagnosis between an ischemic cerebral event and a hemorrhagic cerebral event employing four specific markers . . . does not reasonably provide enablement for a method that measures only two of the markers." Paper No. 23, at page 8, lines 7-11.

Applicant respectfully disagrees with the instant rejection for the reasons of record. However, in an effort to advance prosecution in the subject application, independent Claim 21 has been amended to indicate that the body fluid of a patient is analyzed to detect the presence

and concentration level of myelin basic protein (MBP), the beta isoform of S100 protein (S100), neuronal specific enolase (NSE) and a brain endothelial cell membrane protein. Accordingly, independent Claim 21 and dependent Claims 23-33, 44-45 and 50 are drawn to subject matter that the Examiner acknowledges to be enabled. Withdrawal of the rejection of Claims 21, 23-33, 44-45 and 50 is requested.

Paragraphs 10 and 11: Rejection of Claims 21, 34 and 54-59 Under Obviousness-Type

Claims 21, 34 and 54-59 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-12 of U.S. Patent No. 6,235,489.

Applicant will file a Terminal Disclaimer and a Certificate Under 37 C.F.R. § 3.73(b) upon resolution of the remaining issues, if appropriate.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: July 15, 2003

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

21. (Three Times Amended) A method for [the differential diagnosis] determining the occurrence of a cerebral event and differentially diagnosing between an ischemic cerebral event and a hemorrhagic cerebral event[s] comprising:

a. analyzing a body fluid of a patient to detect presence and concentration level of [one or more] ischemic marker proteins, said ischemic marker proteins [selected from the group] consisting of myelin basic protein (MBP), the beta isoform of S100 protein (S100), and neuronal specific enolase (NSE), said analyzing comprising contacting said MBP, the beta isoform of S100 or NSE [one or more ischemic marker proteins] with a reagent capable of detecting said marker proteins, and removing reagent that does not detect said marker proteins,

b. analyzing a body fluid of said patient to detect presence and concentration level of a brain endothelial cell membrane protein, said analyzing comprising contacting said brain endothelial cell membrane protein with a reagent capable of detecting said endothelial cell membrane protein, and removing reagent that does not detect said brain endothelial cell membrane protein,

c. comparing the concentration level of each protein detected in steps (a) and (b) to specific threshold values to determine the presence of statistically significant concentrations thereof,

d. assessing patient condition by comparing said presence or absence of statistically significant concentrations of said protein[;] in accordance with an analytical flowchart; and

e. determining whether the patient condition assessed in step (d) is an ischemic cerebral event or an hemorrhagic cerebral event, wherein if MBP, S100, NSE and brain endothelial cell membrane proteins are assessed in steps (a) and (b), and only said NSE is elevated, then said patient condition is an ischemic cerebral event; or if MBP, S100, NSE and brain endothelial cell membrane protein are assessed in steps (a) and

(b), and only said brain endothelial cell membrane protein is elevated, then said patient condition is an ischemic cerebral event; or if S100 is present then said patient condition is an ischemic cerebral event; or if NSE along with any of MBP, S100 or a brain endothelial cell membrane protein are present, then said patient condition is an ischemic cerebral event; or if brain endothelial cell membrane protein, with any of MBP, NSE, or S100 are present, then said patient condition is an ischemic cerebral event; or if S100 is present with elevated NSE and normal levels of brain endothelial cell membrane protein, then said patient condition is an ischemic cerebral event; or if S100 is present alone, or along with elevated NSE or brain endothelial membrane protein, then said patient condition is an ischemic cerebral event; or wherein if MBP is present at a level 200 times normal or greater, then said patient condition is a hemorrhagic cerebral event; or if S100 and NSE levels are elevated, and MBP and brain endothelial membrane protein levels are normal, then said patient condition is a hemorrhagic cerebral event; or if S100 and MBP are elevated, then said patient condition is a hemorrhagic cerebral event.

54. (Amended) The method of Claim 21 [34], wherein if MBP, S100, NSE and brain endothelial cell membrane protein are assessed, and only NSE is present, then said ischemic cerebral event is a transitory ischemic attack.

55. (Amended) The method of Claim 21 [34], wherein if MBP, S100, NSE and brain endothelial cell membrane protein are assessed, and only a brain endothelial cell membrane protein is present, then said ischemic cerebral event is a lacunar infarct.

56. (Amended) The method of Claim 21 [34], wherein if S100 is present or if NSE along with any of MBP, S100 or a brain endothelial cell membrane protein are present, or if brain endothelial cell membrane protein, with any one of MBP, NSE, or S100, or if S100 is present with elevated NSE and normal levels of a brain endothelial cell membrane protein, then said ischemic cerebral event is an evolving cerebral infarct.

57. (Amended) The method of Claim 21 [34], wherein if MBP is present at a level about 200 times normal or greater, then said hemorrhagic cerebral event is an intracerebral edema.

58. (Amended) The method of Claim 21 [34], wherein if S100 and NSE are elevated, and MBP and brain endothelial cell membrane protein levels are normal, then said hemorrhagic cerebral event is a subarachnoid hemorrhage.

59. (Amended) The method of Claim 21 [34], wherein if S100 and MBP are elevated, then said hemorrhagic cerebral event is a cerebral edema.